Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.JournalofSurgicalResearch.com

Large-for-size liver transplantation: a flowmetry study in pigs

*Daniel de Albuquerque Rangel Moreira, MD, Ana Cristina Aoun Tannuri, Professor, Alessandro Rodrigo Belon, Biologist, Maria Cecília Mendonça Coelho, Biologist, Josiane Oliveira Gonçalves, Biologist, Suellen Serafini, Biologist, Fabiana Roberto Lima, Biologist, Luciana Orsi Agostini, Biologist, Raimundo Renato Guimarães, Biologist, and Uenis Tannuri, MD**

Pediatric Surgery Division, Pediatric Liver Transplantation Unit and Laboratory of Research in Pediatric Surgery (LIM 30), University of Sao Paulo Medical School, Sao Paulo, Brazil

ARTICLE INFO

Article history:
Received 16 January 2014
Received in revised form
1 March 2014
Accepted 5 March 2014
Available online 12 March 2014

Keywords:
Ischemia–reperfusion
Large-for-size
Liver transplantation
Blood flow
Pig
Experimental
Pediatric liver transplantation

ABSTRACT

Background: Ischemia–reperfusion injury is partly responsible for morbidity in pediatric liver transplantation. Large-for-size (LFS) liver transplantation has not been fully studied in the pediatric population, and the effects of reperfusion injury may be underestimated.

Materials and methods: Thirteen Landrace–Large white pigs weighing 23 kg (range, 17–38 kg) underwent orthotopic liver transplantation. They were divided into two groups according to the size of the donor body: LFS and control (CTRL). After transplantation, the abdominal cavity of the recipient was kept open and portal venous flow (PVF) was measured after 1 h. The ratio of recipient PVF (PVFr) to donor PVF was used to establish correlations with ischemia and reperfusion parameters. Liver biopsies were taken 1 h after transplantation to assess ischemia and reperfusion and to quantify the gene expression of endothelial nitric oxide synthase, interleukin 6, *BAX*, and *BCL*.

Results: Recipient weight, total ischemia time, and warm ischemia time were similar between groups. Among hemodynamic and metabolic analyses, pH, central arteriovenous PCO_2 difference, and AST were statistically worse in the LFS group than in the CTRL group. The same was found with endothelial nitric oxide synthase (0.41 ± 0.18 *versus* 1.56 ± 0.78; $P = 0.02$) and interleukin 6 (4.66 ± 4.61 *versus* 16.21 ± 8.25; $P = 0.02$). In the LFS group, a significant decay in the PVFr was observed in comparison with the CTRL group (0.93 ± 0.08 and 0.52 ± 0.11, respectively; $P < 0.001$).

Conclusions: The implantation of a graft was responsible for poor hemodynamic status of the recipient 1 h after transplantation. Furthermore, the LFS group demonstrated markers of ischemia and reperfusion that were worse when compared with the CTRL group and exhibited a more significant decrease in PVF from donor to recipient.

* *Corresponding author*. Faculdade de Medicina da Universidade de São Paulo, Avenida Dr Arnaldo 455, 4o andar sala 4109, São Paulo—SP, CEP: 01246-903, Brazil. Tel.: +55 11 30812943; fax: +55 11 32556285.
E-mail address: uenist@usp.br (U. Tannuri).

0022-4804/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jss.2014.03.018

1. Introduction

Liver transplantation has been established as a therapy for children with end-stage liver disease. Today, 1-y patient survival rates are approximately 90% [1,2]. Despite ethical dilemmas, pediatric liver transplantation with a living donor provides better quality grafts than organs from cadaveric donors. It is a reasonably available option that entails low risk to the donor [3].

It is sometimes difficult to obtain a graft of ideal size, especially for children weighing less than 10 kg, because of the limitations of the donor surgery. The ideal graft to body weight ratio for liver transplantation ranges from 1%–3%. However, when transplantation is performed in small children, this ratio is >4% in most cases. This situation is known as large-for-size (LFS), characterized by a small abdominal cavity and large graft. Transplanting a large graft into a small abdominal cavity can lead to abdominal compartment syndrome, relatively diminished blood supply, hepatic dysfunction, and long-term morbidity. To avoid these complications, some researchers have used extremely reduced liver grafts (monosegmental grafts); however, there is little evidence of benefit when these grafts are compared with transplants with grafts of the left lateral segment and left lobe, which are more widely used [3,4].

Ischemia–reperfusion injury (IRI) is the main mechanism of acute lesion in transplanted grafts and it contributes to morbidity and mortality in hepatic surgery and transplants. The elements involved in IRI are an inflammatory cascade that culminates in cell death by apoptosis and the cellular mechanisms of regeneration. Apoptosis is a phenomenon that results from the balance between the expression of proapoptotic genes *BAX* and *BAK* and antiapoptotic genes *BCL-2* and *BCL-XL*. The activation of liver regeneration, which is essential for graft survival, is mainly mediated by interleukin 6 (IL-6), an acute phase protein [5].

Nitric oxide synthase (NOS) enzymes produce NO from L-arginine, which is a major pathway of protection against IRI. NO, produced by endothelial NOS (eNOS), provides a protective action mediated by vasodilation and inhibition of platelet aggregation, improving microcirculation, inhibiting the activation of neutrophils, and neutralizing reactive oxygen species produced in IRI.

When the graft to recipient weight ratio (GRWR) is <0.8%, a condition called small-for-size (SFS), we see a portal blood flow that exceeds 300 mL/min/100 g, which plays an important role as a cause of liver aggression. Similarly, in LFS, low portal blood flow may be detrimental and exacerbate the IRI in early transplanted grafts [6,7].

Several prognostic factors have been studied as predictors of the long-term viability of the graft and clinical outcomes after liver transplantation. The hemodynamic status and ability of the recipient to maintain homeostasis after surgery and anesthesia are necessary for proper graft functioning.

The aim of this study was to gain a better understanding of the influence of vascular flow variations and their relation to liver dysfunction and IRI in a porcine LFS liver transplantation model.

2. Methods

2.1. Ethical considerations

All study protocols were approved by the institution's animal welfare regulatory committee, and all protocols conformed with the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health 86-23, revised in 1985. The same team of surgeons, who were experienced in experimental and clinical transplant surgery, performed all procedures. All experiments were performed under general anesthesia, and all animals were euthanized after the experiment.

2.2. Experimental design

Thirteen Landrace–Large white pigs weighing between 17 and 38 kg were randomly divided into control (CTRL) and experimental groups and underwent orthotopic liver transplantation with whole liver grafts. The groups were as follows:

1. CTRL group ($n = 5$): the weight of the donors was equal to the recipients—median 21 kg (range, 17–30 kg).
2. LFS group ($n = 8$): the weight of the donors was nearly two times recipient weight—median 49 kg (range, 33–88 kg).

2.3. Anesthetic procedures and intraoperative monitoring

After a fasting period of 12 h, the animals received an intramuscular injection of xylazine (2 mg/kg) and ketamine (10 mg/kg) as premedication 30 min before the anesthesia. Then, anesthesia was induced with propofol (3–5 mg/kg) and maintained with a continuous infusion of intravenous fentanyl (0.1 μg/kg/min) and isoflurane 1%–2%, titrated to effect. After an open cut down of the right carotid sheath, a single lumen polyurethane catheter was placed in both the internal jugular vein and carotid artery for invasive venous and arterial pressure monitoring, respectively, and fluid administration.

2.4. Donor procedure

A midline incision was performed, and the hepatic ligaments were sectioned, allowing isolation of the suprahepatic and infrahepatic vena cava. Dissection of the hepatic hilum was initiated by ligation of the common bile duct. Then, to place flowmeter probes (model T402; Transonic System, Ithaca, NY), the portal vein was dissected near the entry of the superior pancreatoduodenal vein, and the hepatic artery was dissected near the emergence of the gastroduodenal artery.

The tip of the catheter in the right internal jugular vein was then manually guided to and placed in the suprahepatic vein. The portal vein was punctured with a 22G peripheral catheter (Insyte, BD, Franklin Lakes, NJ). The mean arterial pressure (MAP), suprahepatic vein mean pressure, and portal vein mean pressure were measured, and blood samples were collected from these sites. Blood flow was recorded in the portal vein and hepatic artery. Then, a liver biopsy was taken,